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Synthesis of Functionalized Isobenzomorphans by Two-Step Cyclocondensation of 1,3-Bis(trimethylsilyloxy)-1,3-butadienes with Isoquinolines

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A great variety of functionalized 7,8-benzo-anellated 9-azabicyclo-[3.3.1]nonan-3-ones were prepared by methyl or benzyl chloroformate-mediated condensation of isoquinolines with 1,3-bis(silyloxy)-1,3-butadienes and subsequent TFA-mediated cyclization. The hydroxy group could be functionalized by Suzuki reactions of the corresponding enol triflates. The *N*-benzyloxycarbonyl-substituted products were successfully deprotected. The decarboxylation allowed the synthesis of the parent 7,8-benzo-anellated 9-azabicyclo[3.3.1]nonan-3-ones. The products can be regarded as functionalized isobenzomorphans – simple structural analogues of morphine.

Introduction

The isoquinoline moiety is present in a variety of pharmacologically active alkaloids.[1] Benzylisoquinoline-type alkaloids, such as papaverine or reticuline are isolated from *Papaver*- und *Rauwolfia* plants and show spasmolytic activity.[2] Bis(benzyl)isoquinoline alkaloids include, for example, cycleanine, tetrandrine (antiinflammatory activity), isochondodendrin (sedative activity) and oxyacanthin (sympatholytic activity, adrenalin antagonist).[1] Tubocurarine is the oldest muscle-relaxing agent and its dichloro derivative is used as a narcotic. Phthalidisoquinoline alkaloids, isolated from *Papaveraceae*, are characterized by a tetracyclic system containing a γ-lactone moiety. Important examples are hydrastin and narcotin (noscapin). Hydrastin is used as a blood-stanching agent.[1] Noscapin is used as an antitussivic.[3] Synthetic approaches to tetrahydroisoquinoline alkaloids rely on asymmetric Pictet–Spengler reactions and on Bischler–Napieralski reactions and subsequent enantioselective reduction.[4] Aporphine-alkaloids contain a fused tetracyclic system. For example, apomorphine is used as a strong emetic.[5] Boldine represents a diuretic.[6] Aporphine alkaloids have been prepared, for example, by application of photochemical methods.[7] Pavine and isopavine alkaloids, such as dinorargemonine, eschscholtzine, munitagine and pavine, are isolated from *Papaveraceae*, *Berberidaceae*, *Ranunculaceae*, *Lauraceae* and *Menispermaceae* or from callus cultures of *Cryptocarya chinensis* and are of considerable pharmacological relevance.[1,8] For example, they show activity against *Herpes simplex* virus type 1[9a] and against tumor necrosis factor production.[9b] Pavine-type alkaloids are synthetically available.[10]

Morphine alkaloids represent the most important group of naturally occurring isoquinolines.[1] They have been isolated from opium, a crude product mixture which is produced from *Papaver somniferum*. Important natural products include, for example, morphine, codein, thebaine and heroine[1] which possess a wide range of pharmacological activities (e.g. analgetic, sedative, hypnotic, antitussivic, miotic and antidiuretic activity).[1] Morphine, the structure of which was elucidated by Sir Robert Robinson in 1925,[11] is a very important drug for the treatment of pain. The synthesis of morphine-type alkaloids has been reported.[12]

The development of simpler morphine analogues, which show no dependence-producing and other undesirable side effects, has been the subject of research for many years. Simpler morphine-like compounds include, for example, morphinan and benzomorphan (i.e., 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine).[13] The first synthesis of a benzomorphan has been reported by Barltrop in 1947.[14] The trivial name "benzomorphan" is derived from the trivial name "morphan" (azabicyclo[3.3.1]nonane) (Scheme 1). Positional variation of the nitrogen atom leads to various isomers some of which have been previously synthesized.[15]

Isobenzomorphans (i.e., 7,8-benzo-anellated 9-azabicyclo-[3.3.1]nonanes, 1,2,3,4,5,6-hexahydro-1,5-imino-benzocyclooctenes) represent interesting structural isomers of benzomorphans containing an imino bridge. These compounds are, in a formal sense, simple structural analogues of morphine and are present, for example, in pavine-type

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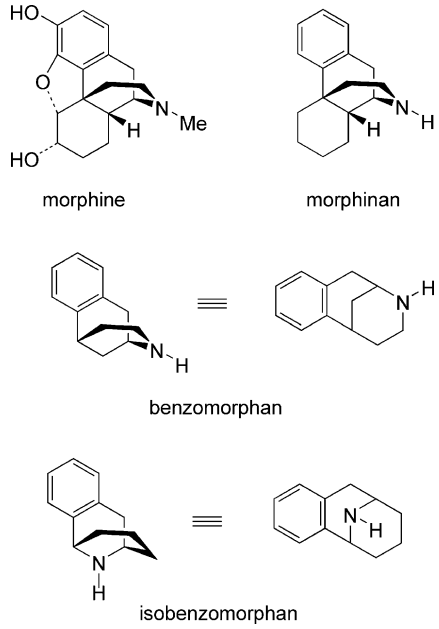
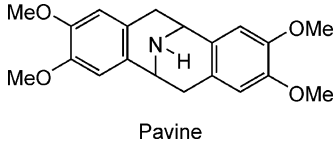


Scheme 1. Morphine and some of its simpler analogues.

alkaloids (Scheme 2). Isobenzomorphans have been prepared by Dieckmann cyclization[16] and by reaction of an acetoneberberine-type enamine with alkyl halides.[17]

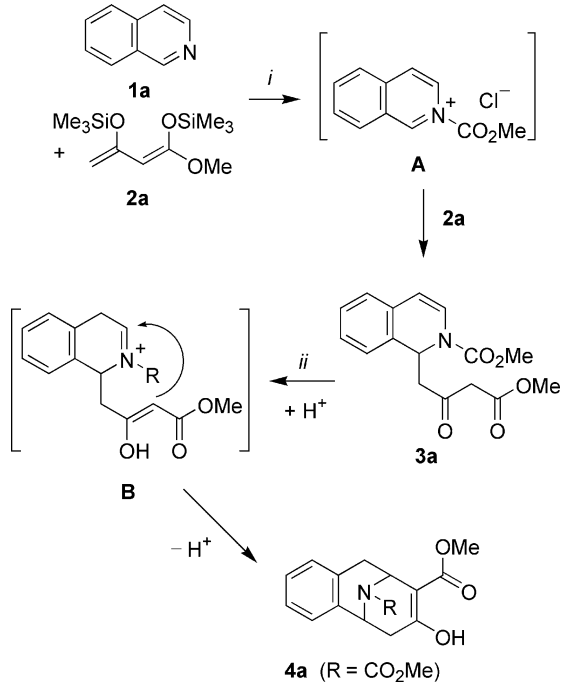


Scheme 2.

Quinolinium- and isoquinolinium salts, generated by alkylation or acylation of quinoline and isoquinoline,[18] are important synthetic building blocks. They have been used, for example, in condensations with Grignard reagents, cyanides (Reissert reaction), (trimethylsilyl)acetonitrile, allylsilanes or silyl enol ethers.[19] In recent years, a number of cyclocondensation reactions of bis(silyl enol ethers) with iminium salts have been reported.[20] Recently, we have reported[21] a convenient approach to 7,8-benzo-anellated 3-hydroxy-9-azabicyclo[3.3.1]non-3-enes (isobenzomorphan derivatives) by condensation of 1,3-bis(silyloxy)-1,3-butadienes[22] with isoquinolinium salts and subsequent acid-mediated cyclization. The products are not readily available by other methods. Herein, we report a comprehensive study of the preparative scope which has been considerably extended with regard to our preliminary communication.[21] In addition, we report, for the first time, the deprotection of the products, the synthesis of parent 7,8-benzo-anellated 9-azabicyclo[3.3.1]nonan-3-ones by decarboxylation, and the functionalization of the hydroxy group by Suzuki reactions of the corresponding enol triflates.

Results and Discussion

The methyl chloroformate-mediated reaction of isoquinoline (**1a**) with 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**2a**), available from methyl acetoacetate,[23] afforded the condensation product **3a** (Scheme 3). The reaction proceeds by formation of the isoquinolinium salt **A** and subsequent regioselective attack of the terminal carbon of **2a**. Treatment of **3a** with TFA afforded the 7,8-benzo-anellated 3-hydroxy-9-azabicyclo[3.3.1]non-3-ene **4a**. The use of TFA proved to be mandatory; employment of hydrochloric acid gave unsatisfactory results. The best yields were obtained when no aqueous work up was carried out. Dichloromethane and TFA were removed in vacuo and the residue was directly purified by chromatography.

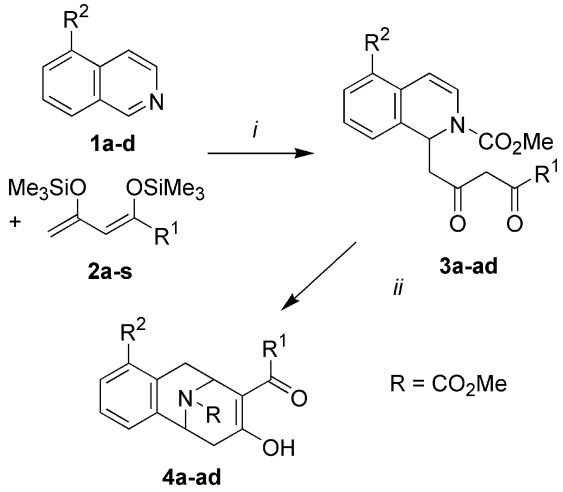


Scheme 3. Possible mechanism of the cyclization of 1,3-bis(silyl enol ether) **2a** with **1a**–**c**: *i*. **1** (1.0 equiv.), **2** (2.0 equiv.), $ClCO_2Me$ (1.2 equiv.), CH_2Cl_2, 0 °C, 2 h, 20 °C, 12 h; *ii*. TFA (2.0 equiv.), CH_2Cl_2, 20 °C, 12 h.

The formation of **3a** proceeds by regioselective attack of the terminal carbon atom of **2a** onto the iminium salt **A** formed by reaction of **1a** with methyl chloroformate. The TFA-mediated cyclization proceeds by formation of the iminium salt **B** and attack of the enol carbon atom onto the latter. The regioselective cyclization can be explained by the higher thermodynamic stability of the iminium cation B compared to the benzylic cation formed by protonation of the other carbon atom of the enamine moiety (by 19.7 kcal/mol at a B3LYP/6-31G* level). Product **4a** is completely present in its enol tautomeric form (which is more stable by 3.3 kcal/mol than the keto form at the same level of theory).

The methyl chloroformate-mediated reaction of **1a**–**d** with 1,3-bis(silyl enol ethers) **2a**–**s**, prepared from the corresponding 1,3-dicarbonyl compounds, afforded the condensation products **3a**–**ad** which were transformed into the 7,8-benzo-anellated 9-azabicyclo[3.3.1]non-3-enes **4a**–**ad** (Scheme 4, Table 1). All reactions proceeded in moderate to excellent yields. Regarding the cyclization step, better yields were generally obtained for substrates derived from 1,3-di-

ketones compared to those derived from β-keto esters. This can be explained by the higher extent of enolization of 1,3-diketones compared to β-keto esters which is important for the TFA-mediated cyclization step. Noteworthy, synthesis and reactions of the pyridine- and thiophene-derived 1,3-bis(silyl enol ethers) **2w** and **2x** have not yet been reported.



Scheme 4. Synthesis of **4a**–**ad**: *i*. **1** (1.0 equiv.), **2** (2.0 equiv.), $ClCO_2Me$ (1.2 equiv.), CH_2Cl_2, 0 °C, 2 h, 20 °C, 12 h; *ii*. TFA (2.0 equiv.), CH_2Cl_2, 20 °C, 12 h.

Table 1. Synthesis of **4a**–**ad**.

1	2	3,4	R^1	R^2	% 3[a]	% 4[a]
a	**a**	**a**	OMe	H	83	37
a	**b**	**b**	Me	H	80	57
a	**c**	**c**	$O(CH_2)_2OMe$	H	79	25
a	**d**	**d**	CH_2OMe	H	55	69
a	**e**	**e**	Ph	H	76	85
a	**f**	**f**	*t*Bu	H	86	71
b	**b**	**g**	Me	NO_2	92	83
b	**g**	**h**	OEt	NO_2	94	47
b	**e**	**i**	Ph	NO_2	94	93
c	**b**	**j**	Me	Br	73	89
c	**g**	**k**	OEt	Br	90	60
c	**e**	**l**	Ph	Br	88	94
a	**h**	**m**	4-$(NO_2)C_6H_4$	H	43	60
a	**i**	**n**	4-ClC_6H_4	H	70	69
a	**j**	**o**	4-FC_6H_4	H	68	67
a	**k**	**p**	2-$(MeO)C_6H_4$	H	68	69
a	**l**	**q**	2-MeC_6H_4	H	43	72
d	**m**	**r**	2-FC_6H_4	Et	76	81
a	**n**	**s**	2-ClC_6H_4	H	58	78
d	**o**	**t**	1-naph	Et	41	77
a	**p**	**u**	2-naph	H	76	70
a	**q**	**v**	3,4,5-$(MeO)_3C_6H_2$	H	34	55
a	**r**	**w**	2-pyridyl	H	68	27
a	**s**	**x**	2-thienyl	H	22	34
b	**i**	**y**	4-ClC_6H_4	NO_2	54	75
b	**j**	**z**	4-FC_6H_4	NO_2	72	55
b	**l**	**aa**	2-MeC_6H_4	NO_2	71	96
b	**m**	**ab**	2-FC_6H_4	NO_2	41	86
b	**n**	**ac**	2-ClC_6H_4	NO_2	56	60
b	**p**	**ad**	2-naph	NO_2	56	63

[a] Yields of isolated products.

All structures were proved by spectroscopic methods. Noteworthy, the ^1H and ^{13}C NMR spectra show a splitting of several signals, due to dynamic processes of the carbamate moiety possessing a significant double bond character. The structures of **3e**, **4e**, **4p**, and **4r** were independently confirmed by X-ray crystal structure analyses (Figure 1 and Figure 2).[24]

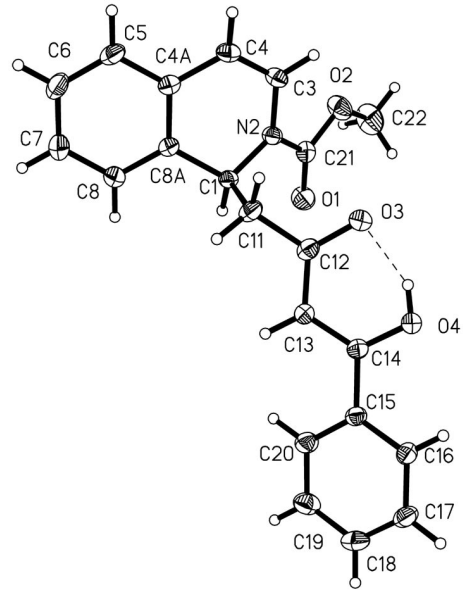


Figure 1. ORTEP plot of **3e**. The thermal ellipsoids of 50% probability are shown for the non-hydrogen atoms.

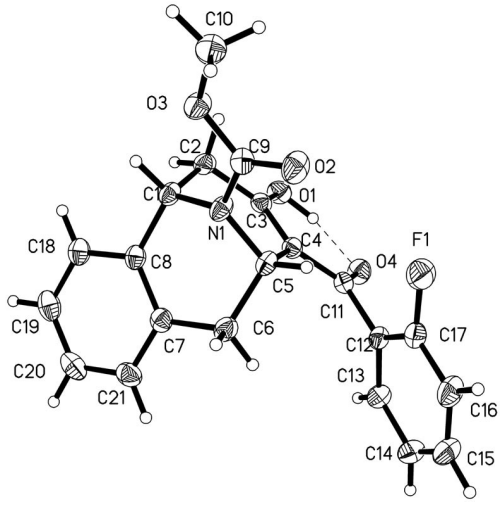
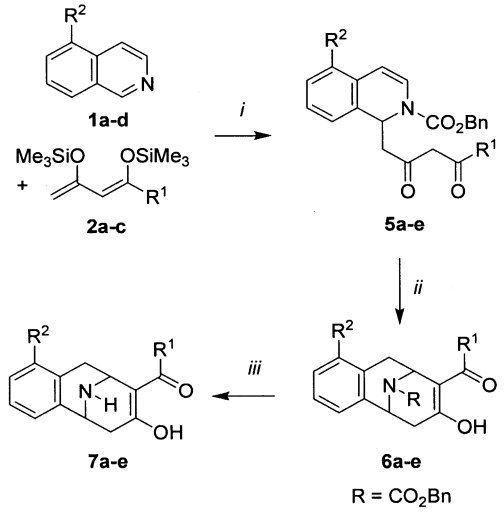


Figure 2. ORTEP plot of **4r**. The thermal ellipsoids of 50% probability are shown for the non-hydrogen atoms.

The reaction of **1a**–**d** with 1,3-bis(silyl enol ethers) **2a**–**c**, in the presence of *benzyl* chloroformate, afforded the condensation products **5a**–**e** which were transformed into the 7,8-benzo-anellated 9-azabicyclo[3.3.1]non-3-enes **6a**–**e** (Scheme 5, Table 2). While all attempts to deprotect the methoxycarbonyl-substituted products **4a**–**ad** proved to be

unsuccessful, the deprotection (H_2, Pd/C) of benzyloxycarbonyl-substituted derivatives **6a**–**e** was possible and gave the desired products **7a**–**e**. The hydrogenation of **6b** resulted not only in cleavage of the protective group, but also in transformation of the nitro into an amino group. As expected, no splitting of signals was observed for all products **7a**–**e**, due to the absence of the carbamate moiety.



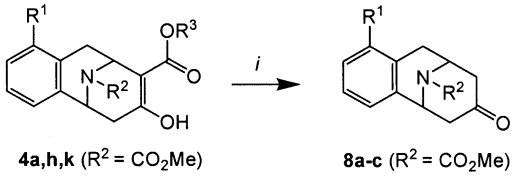
Scheme 5. Synthesis of **7a**–**e**: *i.* **1** (1.0 equiv.), **2** (2.0 equiv.), $ClCO_2Bn$ (1.2 equiv.), CH_2Cl_2, 0 °C, 2 h, 20 °C, 12 h; *ii.* TFA (2.0 equiv.), CH_2Cl_2, 20 °C, 12 h; *iii.* MeOH, Pd/C (10 mol-%), 24 h, 20 °C.

Table 2. Synthesis of **7a**–**e**.

1	2	5,6,7	R^1	R^2	% **5**[a]	% **6**[a]	% **7**[a]
a	**a**	**a**	OMe	H	83	37	37
b	**a**	**b**	OMe	NO_2	97	37	
b	**a**	**b**	OMe	NH_2			37
c	**b**	**c**	Me	Br	79	25	25
a	**c**	**d**	$O(CH_2)_2OMe$	H	80	57	57
a	**b**	**e**	Me	H	55	69	69

[a] Isolated yields.

Stirring of a DMSO solution of **3a**,**h**,**k** in the presence of LiCl[25] at 130 °C resulted in decarboxylation and formation of the 7,8-benzo-anellated 9-azabicyclo-[3.3.1]nonan-3-ones **8a**–**c** (Scheme 6, Table 3). The structures of **8a** and **8b** were independently confirmed by X-ray crystal structure analysis (Figure 3).[24]



Scheme 6. Synthesis of **8a**–**c**: *i.* LiCl, DMSO/H_2O, 130 °C, 8 h.

Product **4d** was transformed into its triflate **9**. The Suzuki reaction of the latter with phenyl-, 4-methoxyphenyl-, and 4-(trifluoromethyl)boronic acid afforded

Table 3. Synthesis of **8a**–**c**.

4	8	R^1	R^2	R^3	% **8**[a]
a	**a**	H	CO_2Me	Me	46
h	**b**	NO_2	CO_2Me	Et	44
k	**c**	Br	CO_2Me	Et	62

[a] Isolated yields.

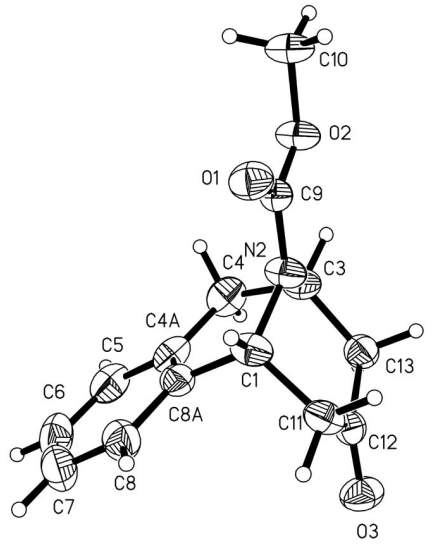
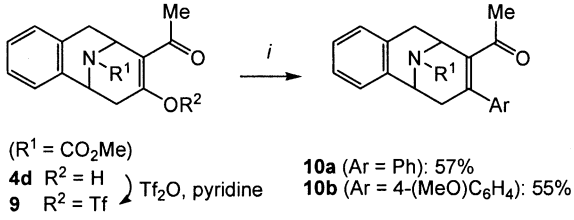


Figure 3. Ortep plot of **8a**. The thermal ellipsoids of 50% probability are shown for the non-hydrogen atoms.



Scheme 7. Synthesis of **10a**,**b**: *i.* 1) **4d** (1.0 equiv.), Tf_2O (1.2 equiv.), pyridine (2.0 equiv.), CH_2Cl_2, –78 to 20 °C, 4 h; 2) **9** (1.0 equiv.), $ArB(OH)_2$ (1.3 equiv.), K_3PO_4 (1.6 equiv.), $Pd(PPh_3)_4$ (0.03 equiv.), 1,4-dioxane, reflux, 20 h.

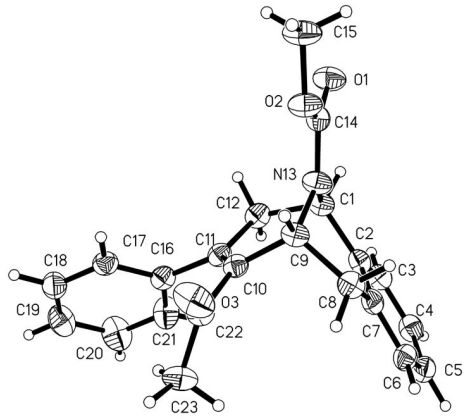


Figure 4. Ortep plot of **10a**. The thermal ellipsoids of 50% probability are shown for the non-hydrogen atoms.

the isobenzomorphans **10a** and **10b**, respectively (Scheme 7). The structures of **10a** and **10b** were independently confirmed by X-ray crystal structure analyses (Figure 4).[24]

Conclusions

A great variety of functionalized 7,8-benzo-anellated 9-azabicyclo-[3.3.1]nonan-3-ones were prepared by methyl or benzyl chloroformate-mediated condensation of isoquinolines with 1,3-bis(silyloxy)-1,3-butadienes and subsequent TFA-mediated cyclization. The hydroxy group could be functionalized by Suzuki reactions of the corresponding enol triflates. The *N*-benzyloxycarbonyl-substituted products were successfully deprotected. The decarboxylation allowed the synthesis of the parent 7,8-benzo-anellated 9-azabicyclo[3.3.1]nonan-3-ones. The products can be regarded as functionalized isobenzomorphans – simple structural analogues of morphine.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were taken in $CDCl_3$ at 250, 300, and 500 MHz, respectively. Chemical shifts are reported in parts per million using the solvent internal standard (chloroform, 7.26 and 77.0 ppm, respectively). Infrared spectra were recorded on a FTIR spectrometer. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, isobutane) or electrospray ionization (ESI). Melting points are uncorrected. CH_2Cl_2 (anhydrous, 99.8%) was purchased directly from ACROS and used without further purification. Analytical thin layer chromatography was performed on 0.20 mm 60 A silica gel plates. Column chromatography was performed on 60 A silica gel (60–200 mesh). All cyclization reactions were carried out in Schlenk flasks in dried solvents under argon. Crystallographic data were collected on a Bruker X8Apex with Mo-K_α radiation (λ = 0.71073 Å). Data of **4p** were collected on a STOE IPDS II. The structures were solved by direct methods using SHELXS-97 and refined against F^2 on all data by full-matrix least-squares with SHELXL-97. All non-hydrogen atoms were refined anisotropically, all hydrogen atoms (for **4p** except for the H atom attached to oxygen) were refined in the model at geometrically calculated positions and refined by using a riding model.

General Procedure for the Synthesis of 3a–ad and 5a–e: To a CH_2Cl_2 solution (40 mL) of isoquinoline (0.520 g, 4.0 mmol) was added the 1,3-bis-silyl enol ether (8.0 mmol) and methyl or benzyl chloroformate (0.460 g, 4.8 mmol) at 0 °C. The solution was stirred for 2 h at 0 °C and for 12 h at 20 °C. A saturated aqueous solution of ammonium chloride (20 mL) was added and the organic and the aqueous layers were separated. The latter was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptanes → heptanes/EtOAc, 2:1).

Methyl 1-[(*Z*)-2-Hydroxy-4-methoxy-4-oxo-2-butenyl]isoquinoline-2(1*H*)-carboxylate (3a): Starting with isoquinoline (0.520 g, 4.00 mmol), **2a** (2.080 g, 8.00 mmol) and methyl chloroformate (0.460 g, 4.80 mmol), **3a** was prepared as an orange oil (1.000 g, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.25–2.41 (m, 1 H, NCHCH_2, enol), 2.52–2.62 (m, 1 H, NCHCH_2, enol), 2.76 (dd, ^3J = 6.8, ^2J = 14.4 Hz, 1 H, NCHCH_2, keto), 2.97 (dd, ^3J = 6.8, ^2J = 14.4 Hz, 1 H, NCHCH_2, keto), 3.29–3.56 (m, 2 H, $COCH_2CO$, keto), 3.66 (s, 3 H, OCH_3, keto, rotamer), 3.68 (s, 3 H, OCH_3, keto-enol, rotamer), 3.69 (s, 3 H, OCH_3, keto-enol, rotamer), 3.79 (s, 3 H, OCH_3, keto, rotamer), 3.85 (s, 3 H, OCH_3, keto-enol, rotamer), 4.79 (s, 1 H, COHC*H*CO, enol), 5.61–5.98 (m, 2 H, NC*H*CH_2, NCHC*H*), 6.77–6.96 (m, 1 H, NC*H*CH), 7.05–7.28 (m, 4 H, Ar), 11.91, 11.98 (s, 1 H, OH, rotamer) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 39.8, 40.3 (NCH*C*H_2, enol, rotamer), 47.5 (NCH*C*H_2, keto), 49.2, 49.7 (CO*C*H_2CO, keto), 51.0, 51.6, 51.7 (N*C*HCH_2, keto-enol, rotamer), 52.2, 53.0, 53.3, 53.8 (OCH_3, keto-enol, rotamer), 91.2 (CO*C*HCOH, enol), 108.7, 109.0 (NCH*C*H, keto-enol, rotamer), 124.1, 124.6, 124.7, 125.9, 126.1, 126.3, 126.9, 127.0, 127.2, 128.0 (N*C*HCH, CH_{Ar}, keto-enol, rotamer), 129.7, 131.1 (C_{Ar}), 153.1, 153.3 (NCOO, keto-enol, rotamer), 166.9, 167.3, 172.5, 173.5, 173.8 (CH_2*C*OO, COH, keto-enol, rotamer), 199.5 (NCHCH_2*C*O) ppm. IR (neat): $\tilde{\nu}$ = 2956 (w), 1714 (s), 1634 (s), 1571 (w), 1447 (s), 1415 (m), 1353 (s), 1328 (s), 1290 (m), 1242 (s), 1200 (s), 1153 (m), 1124 (m), 1025 (w), 981 (w), 949 (w), 775 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 303 (2) [M$^+$], 255 (5), 188 (100), 144 (37), 129 (11), 103 (8), 60 (8). HRMS (EI): = $C_{16}H_{17}NO_5$ [M$^+$] 303.1101; found 303.1103.

Benzyl 1-(3-Methoxycarbonyl-2-oxopropyl)isoquinoline-2(1*H*)-carboxylate (5a): Starting with isoquinoline (0.516 g, 4.00 mmol), **2a** (2.112 g, 8.00 mmol) and benzyl chloroformate (0.819 g, 4.80 mmol), **5a** was prepared as a pale yellow solid (1.099 g, 72%, m.p. 98–100 °C). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.67–2.81 (m, 1 H, NCHCH_2), 2.93–3.04 (m, 1 H, NCHCH_2), 3.37 (s, 2 H, $COCH_2$, isomer 1), 3.50 (s, 2 H, $COCH_2$, isomer 2), 3.61 (s, 3 H, CO_2CH_3, isomer 1), 3.66 (s, 3 H, CO_2CH_3, isomer 2), 5.21 (s, 2 H, NCO_2CH_2, isomer 1), 5.25 (s, 2 H, NCO_2CH_2, isomer 2), 5.80–5.97 (m, 2 H, NCH, =CH), 6.82 (d, ^3J = 7.7 Hz, 1 H, =CH, isomer 1), 6.84 (d, ^3J = 7.7 Hz, 1 H, =CH, isomer 2), 7.04–7.35 (m, 9 H, Ar) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 47.7, 49.4 (CH_2), 51.8 (OCH_3), 52.3 (N*C*HCH_2), 68.2 (CO_2*C*H_2), 108.9 (NCH*C*H), 124.2 (N*C*HCH), 124.9, 125.0, 126.5, 127.4, 128.1, 128.4, 128.6 (Ar-CH), 129.8 131.2, 135.7, 152.6, 167.4, 199.6 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2949 (w), 1758 (m), 1702 (s), 1632 (m), 1452 (m), 1417 (s), 1388 (s), 1350 (s), 1323 (s), 1276 (s), 1241 (s), 1191 (m), 1119 (s), 1073 (s), 1028 (m), 1008 (m), 984 (s), 945 (m), 778 (s), 757 (s), 736 (s), 695 (s), 577 (m), 551 (m), 529 (s) cm^{-1}. HRMS (TOF): *m*/*z* (%) calcd. for $C_{22}H_{21}NO_5Na^+$ ([M + Na]$^+$): 402.13119, found: 402.13055. $C_{22}H_{21}NO_5$ (379.41): calcd. C 69.64, H 5.58, N 3.69; found C 70.01, H 5.68, N 3.47.

General Procedure for the Synthesis of 4a–Ad and 6a–e: To a CH_2Cl_2 solution (6 mL) of **3** or **5** (1.5 mmol) was added TFA (3.0 mmol) and the solution was stirred for 12 h at 20 °C. The solution was concentrated in vacuo and the residue was purified by chromatography (silica gel, hexane → hexane/EtOAc, 2:1). The product was dried for 16 h at 50 °C and 0.01 mbar to remove hydrolyzed **2**. Due to the amide resonance and formation of *E*/*Z*-isomers, doubling of some signals was observed. In all products, the 1,3-dicarbonyl moiety resides in the enolic form.

Methyl 11-Hydroxy-13-(1-methoxyvinyl)-13-azatricyclo[7.3.1.0^{2,7}]-trideca-2,4,6,10-tetraene-10-carboxylate (4a): Starting with **3a** (0.735 g, 2.40 mmol), dichloromethane (12 mL) and TFA (0.550 g, 4.80 mmol), **4a** was isolated as a colorless solid (0.270 g, 37%, m.p. 117–119 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.35 (2d, ^2J = 17.8 Hz, 1 H, CH_2COH, rotamer), 2.83 (d, ^2J = 16.6 Hz, 1 H, CH_2C_{Ar}), 2.94–3.07 (m, 1 H, CH_2COH), 3.19–3.29 (m, 1 H, CH_2C_{Ar}), 3.73, 3.75 (s, 3 H, OCH_3, rotamer), 3.81, 3.82 (s, 3 H, OCH_3, rotamer), 5.26 (d, ^3J = 5.5 Hz, 1 H, NC*H*CO, rotamer),

5.36 (d, ^3J = 6.2 Hz, 1 H, NC*H*C_{Ar}, rotamer), 5.39 (d, ^3J = 5.5 Hz, 1 H, NC*H*CCO, rotamer), 5.48 (d, ^3J = 6.2 Hz, 1 H, NCH_{Ar}, rotamer), 7.07–7.19 (m, 4 H, Ar), 12.05 (s, 1 H, OH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 33.4, 33.9 (*C*H_2C_{Ar}, rotamer), 36.9, 37.3 (*C*H_2COH, rotamer), 44.5, 45.0 (N*C*HCCO, rotamer), 48.5, 49.2 (N*C*HC_{Ar}, rotamer), 51.7 (OCH_3), 52.8 (OCH_3), 99.6, 99.9 (*C*COO, rotamer), 126.3, 126.6, 127.3, 127.4, 129.5, 129.8 (CH_{Ar}, rotamer), 132.1, 132.5, 136.1, 136.3 (C_{Ar}, rotamer), 154.3, 154.4 (N*C*OO, rotamer), 170.0 (COH), 170.6, 170.8 (C*C*OO, rotamer) ppm. IR (KBr): $\tilde{\nu}$ = 2954 (br., w), 1601 (s), 1617 (m), 1413 (m), 1385 (w), 1334 (s), 1098 (m), 1265 (m), 1221 (s), 1115 (m), 1066 (m), 1021 (m), 819 (w), 766 (m), 673 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 303 (36) [M$^+$], 212 (100), 188 (12), 180 (13), 116 (6), 114 (7). $C_{16}H_{17}NO_5$ (303.31): calcd. C 63.36, H 5.65, N 4.62; found C 63.49, H 5.97, N 4.81.

10-Methyl 13-Benzyl 11-Hydroxy-13-azatricyclo[7.3.1.0^{2,7}]trideca-2,4,6,10-tetraene-10,13-dicarboxylate (6a): Starting with **5a** (0.997 g, 2.63 mmol) and TFA (0.600 g, 5.26 mmol), **6a** was isolated as a colourless solid (0.340 g, 34%, m.p. 54–56 °C). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.35 (dd, ^2J = 17.9, ^3J = 7.1 Hz, 1 H, NCHC*H*$_2$), 2.78–3.32 (m, 3 H, NCHC*H*$_2$), 3.81 (s, 3 H, CO_2CH_3), 5.07–5.26 (m, 2 H, CO_2CH_2), 5.29–5.51 (m, 2 H, NCH), 7.06–7.21 (m, 4 H, Ar), 7.31–7.37 (m, 5 H, Ar), 12.05 (s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.6/34.0, 37.1/37.5 (NCH*C*H$_2$), 44.6/45.2, 48.7/49.3 (NCH), 51.7 (CO_2CH_3), 67.3/67.5 (CO_2CH_2), 99.6/100.1 (C), 126.3/126.4, 126.6, 127.4/127.5, 127.9, 128.1/128.2, 128.5, 129.6/129.9 (Ar-CH), 132.2/132.6, 136.1/136.3, 136.5, 153.8/153.9, 170.0, 170.7/170.9 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2951 (w), 1697 (s), 1655 (s), 1614 (m), 1496 (w), 1424 (s), 1321 (s), 1295 (s), 1257 (s), 1217 (s), 1201 (s), 1113 (s), 1096 (s), 1063 (s), 1014 (s), 976 (m), 811 (m), 758 (s), 734 (s), 693 (s), 670 (s), 624 (m), 611 (m), 591 (m), 572 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 379 (26) [M$^+$], 288 (33), 244 (49), 212 (39), 91 (100). HRMS (EI): calcd. for $C_{22}H_{21}NO_5$ (M$^+$): 379.14142; found: 379.14077.

General Procedure for the Synthesis of 7a–e: To a stirred methanol suspension (25 mL) of Pd/C (0.1 equiv.) was added **6a**–**e** (1.0 equiv.). The reaction mixture was set under hydrogen atmosphere and stirred for 24 h at 20 °C. The reaction mixture was filtered (celite) and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptanes → heptanes/EtOAc, 0:1).

Methyl 11-Hydroxy-13-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-10-carboxylate (7a): Starting with **6a** (0.275 g, 0.72 mmol), **7a** was isolated as a pale yellow solid (0.150 g, 85%), m.p. 134–135 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.31 (dd, ^2J = 17.9, ^3J = 1.1 Hz, 1 H, NCHC*H*$_2$), 2.80 (d, ^2J = 16.8 Hz, 1 H, NCHC*H*$_2$), 2.92 (dd, ^2J = 17.9, ^3J = 6.1 Hz, 1 H, NCHC*H*$_2$), 3.16 (dd, ^2J = 16.8, ^3J = 5.6 Hz, 1 H, NCHC*H*$_2$), 3.79 (s, 3 H, CO_2CH_3), 4.27 (d, ^3J = 5.5 Hz, 1 H, NCH), 4.37 (d, ^3J = 6.0 Hz, 1 H, NCH), 7.02–7.18 (m, 4 H, Ar), 11.89 (br. s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.7, 38.2 (NCH*C*H$_2$), 45.2, 49.8 (NCH), 51.5 (CO_2CH_3), 101.2 (C), 126.1, 126.7, 127.0, 129.8 (Ar-CH), 132.8, 138.3, 170.4, 171.2 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3314 (w), 3214 (w), 2925 (w), 1651 (s), 1609 (s), 1442 (s), 1417 (m), 1377 (m), 1347 (m), 1327 (m), 1291 (s), 1264 (s), 1244 (m), 1215 (s), 1197 (s), 1074 (s), 986 (m), 849 (m), 834 (s), 815 (s), 792 (m), 775 (s), 758 (s), 738 (s), 675 (m), 635 (m), 588 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 245 (19) [M$^+$], 154 (97), 129 (91), 57 (100), 43 (91). HRMS (EI): calcd. for $C_{14}H_{15}NO_3$ (M$^+$): 245.10464, found 245.10539. $C_{14}H_{15}NO_3$ (245.27): calcd. C 68.56, H 6.61, N 5.71; found C 68.48, H 6.12, N 5.38.

General Procedure for the Decarboxylation of 4a,h,k: To a solution of **9** (1.40 mmol) in wet DMSO (13 mL, 2% of water) was added LiCl (2.94 mmol) and the solution was stirred for 8 h at 130 °C. After cooling to 20 °C, CH_2Cl_2 (30 mL) was added and the mixture was washed with water (1 × 20 mL) and brine (1 × 20 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptanes → heptanes/EtOAc, 2:1).

Methyl 11-Oxo-13-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene-13-carboxylate (8a): Starting with **6a** (0.418 g, 1.40 mmol) and LiCl (0.125 g, 2.94 mmol) in DMSO (13 mL, 2% water), **8a** was isolated as a colourless solid (0.159 g, 46%); m.p. 127–130 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.37 (m, 1 H, $COCH_2$), 2.49 (m, 1 H, $COCH_2$), 2.68–2.91 (m, 3 H, $COCH_2$, NCHC*H*$_2$C$_{Ar}$), 3.36 (br.dd, ^2J = 17.7, ^3J = 6.1 Hz, 1 H, NCHC*H*$_2$C$_{Ar}$), 3.80 (s, 3 H, OCH_3), 5.07 (br. m, ^3J = 6.1 Hz, 1 H, NC*H*CH$_2$C$_{Ar}$, rotamers), 5.20 (br. m, 1 H, NC*H*CH$_2$C$_{Ar}$, rotamers), 5.58 (br. m, 1 H, COCH$_2$C*H*C$_{Ar}$, rotamers), 5.70 (br. m, 1 H, COCH$_2$C*H*C$_{Ar}$, rotamers), 7.03–7.07 (br. m, 2 H, Ar), 7.15–7.19 (m, 2 H, Ar) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 33.6, 33.9 (CH_2, rotamers), 46.7, 46.9 (CH_2, rotamers), 47.1, 47.6 (NCH, rotamers), 48.9, 49.2 (CH_2, rotamers), 51.6, 51.9 (NCH, rotamers), 53.1 (OCH_3), 126.2, 126.5, 127.0, 127.8, 129.3, 129.6 (CH_{Ar}, rotamers), 130.4, 130.8, 135.2, 135.4 (C_{Ar}, rotamers), 154.9 (NCOO), 206.9 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 3048 (w), 3005 (w), 2956 (w), 2933 (w), 2908 (w), 2852 (w), 1712 (s), 1693 (s), 1493 (w), 1455 (s), 1412 (s), 1347 (m), 1326 (m), 1279 (m), 1220 (m), 1208 (m), 1119 (m), 1045 (m), 989 (w), 763 (m), 682 (w) cm–1. MS (EI, 70eV): *m*/*z* (%) = 245 (20) [M+], 202 (4), 188 (100), 144 (31), 128 (12), 115 (13), 91 (4), 77 (3), 59 (4). $C_{14}H_{15}NO_3$ (245.27): calcd. C 68.56, H 6.16, N 5.71; found C 68.23, H 6.35, N 5.39.

Synthesis of 9 and of 10a–c: To a CH_2Cl_2 solution of **4d** (2.80 mmol) was added pyridine (5.60 mmol) at –78 °C. To the solution was added dropwise trifluoromethanesulfonic acid anhydride (3.36 mmol) at –78 °C. The solution was warmed to 20 °C during 4 h with stirring. The solvent was removed in vacuo and the residue was purified by chromatography (silica gel, heptanes → heptanes/EtOAc, 2:1) to give **9**. The product was dried in vacuo and directly used for the synthesis of **10a**–**c**. To a 1,4-dioxane solution (2.5 mL) of **9** (1.00 mmol) were added the boronic acid (1.30 mmol), potassium phosphate (1.60 mmol) and tetrakis(triphenylphosphane)palladium(0) (0.03 mmol) at 20 °C. The solution was stirred under reflux for 20 h. After cooling to 20 °C, an aqueous solution of ammonium chloride was added (3 mL) and to the mixture was added CH_2Cl_2 (15 mL). The organic and the aqueous layer were separated and the latter was extracted with CH_2Cl_2 (20 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptane → heptane/EtOAc, 2:1).

Methyl 10-Acetyl-11-phenyl-13-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-13-carboxylate (10a): Starting with **4d** (0.804 g, 2.80 mmol), pyridine (0.443 g, 5.6 mmol) and trifluoromethanesulfonic anhydride (0.948 g, 3.36 mmol) in CH_2Cl_2 (28 mL), **9** was isolated as a slightly yellow oil (0.906 g, 77%). Starting with **9** (0.419 g, 1.00 mmol), phenylboronic acid (0.159 g, 1.30 mmol), potassium phosphate (0.340 g, 1.60 mmol) and tetrakis(triphenylphosphane)palladium(0) (0.035 g, 0.03 mmol) in 1,4-dioxane (2.5 mL), **10a** was isolated as a colourless solid (0.197 g, 57%); m.p. 97–98 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.55, 1.56 (s, 3 H, $COCH_3$, rotamers), 2.21, 2.24 (s, 3 H, $COCH_3$, rotamers), 2.66 (m, 2 H, CH_2), 3.13 (m, 2 H, CH_2), 3.68, 3.74, 3.76 (s, 3 H, OCH_3), 5.27–5.59 (m, 2 H, NCH), 6.97–7.00 (m, 2 H, Ar), 7.07–7.20 (m, 5 H, Ar), 7.27–7.29 (m, 2 H, Ar), 7.45 (m, 1 H, Ar) ppm. ^{13}C NMR

(75.5 MHz, $CDCl_3$): δ = 31.0 ($CO\mathit{C}H_3$), 33.0, 33.3, 34.7, 34.9 (CH_2, rotamers), 40.8, 41.1 (CH_2, rotamers), 47.4, 47.8, 49.0, 49.7, 50.0, 50.7, 51.3, 51.5, 52.7 (NCH, OCH_3, rotamers), 126.2, 126.4, 126.5, 127.2, 127.6, 127.7, 128.6, 129.3, 129.6 (CH_{Ar}, rotamers), 132.4, 132.9, 136.8, 136.9, 137.8, 138.0, 140.6, 142.5, 143.1, 144.4 (C_{Ar}, *C*CO, $\mathit{C}C_{Ar}$, rotamers), 154.3, 154.5 (NCOO, rotamers), 202.3, 202.6 ($\mathit{C}OCH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3021 (w), 2953 (w), 2886 (w), 2847 (w), 1693 (s), 1672 (s), 1628 (w), 1491 (w), 1453 (s), 1415 (m), 1352 (m), 1334 (m), 1323 (m), 1286 (w), 1251 (m), 1236 (m), 1190 (w), 1119 (m), 1029 (m), 764 (m), 745 (m), 705 (m) cm^{-1}. MS (EI, 70eV): *m*/*z* (%) = 347 (100) [M^+], 304 (10), 288 (23), 272 (36), 256 (83), 229 (50), 215 (8), 204 (22), 188 (74), 115 (11), 59 (4). $C_{22}H_{21}NO_3$ (347.41): calcd. C 76.06, H 6.09, N 4.03; found C 75.78, H 6.16, N 3.87.

Supporting Information (see footnote on the first page of this article): ORTEP plots of **4p**, **8b** and **10b**, experimental procedures and characterization of all new compounds.

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